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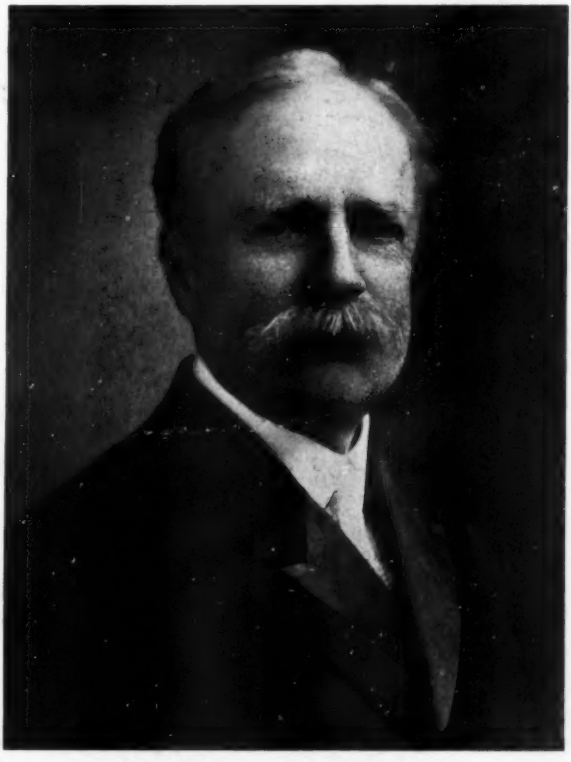

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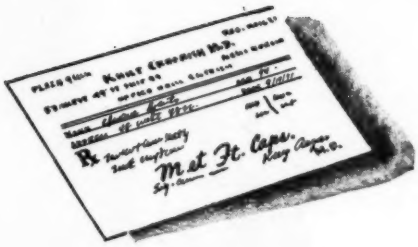

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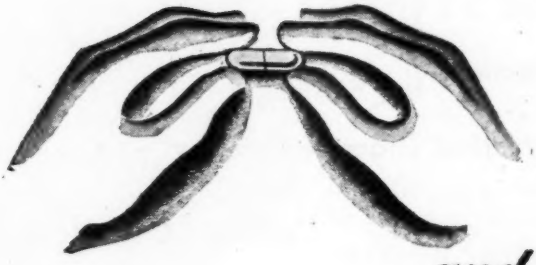

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*Kamman, G. R.: Fatigue as a Symptom in Depressed Patients, Journal-Lancet 65:238 (July) 1945.

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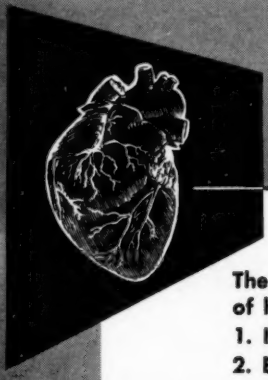

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AND THE SCIENCES SUPPORTING PUBLIC HEALTH

Since 1825

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CONTENTS

E D I T O R I A L

INSULIN AND THE PROBLEM OF PRICES.

A HEADLINE in a recent issue of a metropolitan newspaper reads as follows: "Insulin Cost Worries Doctors". The article continues by pointing out that there was a recent increase in the price of insulin amounting to fifty per cent. This increase is claimed to work a hardship on low income families which have members suffering from diabetes.

We agree that this increase works some hardship on those with fixed low incomes but what increase in the cost of living doesn't and just why should this specific article be singled out as deserving special attention? Possibly the drug industry has set such a fine example of voluntary price control, even to the extent of lowering costs to the consumer, that this increase by comparison seems harsh. The reasons for the price increase for insulin justify the case. The cost of raw material, the fresh pancreas from animals, has gone up partly due to increased packing house costs and partly because of the demand for it in the manufacture of protein hydrolysates. Insulin manufacturers have absorbed these increased costs for a long time until the rise could no longer be postponed. In terms of actual increase the average patient's insulin cost may go up from about five to ten cents daily.

From the purely emotional viewpoint a wonderful case can be prepared depicting the mercenary drug manufacturer victimizing the hapless diabetic by charging exhorbitant prices for an indispensable drug. From careful analysis, however, it is clear that hundreds of other instances of hardships just as severe might be cited. Cases involving food, clothing, and other necessities are just as relevant as the single instance of a drug product and practically all food and clothing prices have risen fifty per cent. The truth is that these two items alone account for most of our increased cost of living.

What is the answer? Labor tells us that prices must come down or wages must go up. Industry sees the only cure in lower wages which will then make lower prices possible. Which side is right?

The trouble in America today is that its people, labor as well as management and all others have fallen into a way of life and a philosophy of behavior that, if not corrected, will eventually destroy our country. That philosophy of each man for himself and the devil take the hindmost has been so universally adopted it is small wonder that we suffer from economic, social and political confusion. No form of government, most of all a democracy, can long endure with its people dedicated to such a way of life; no business can succeed, no cultural or social growth can take place and the final result if pursued to the bitter end will be anarchy, dictatorship and totalitarianism.

Those industrialists who believe that labor and the consumer are to be exploited as far as possible and those in labor who seek only their own advancement regardless of its effect on others both must learn the same lesson. All of us need to realize that if each man takes every possible advantage of his fellow-man we will soon become a pack of snarling savage animals. There is not one of us who is completely independent of everyone else for his own safety and comfort. Think of what life would be like if we could trust no one. Just as we must depend on someone, others depend on us and the "Golden Rule" is still a perfect guide for human behavior in business as well as social conduct.

What America needs is political leaders who will think of the country rather than the next election, industrialists who recognize the hardships that high prices bring and labor leaders who will teach their men responsibility rather than incite them with orations of class hatred. Only by teamwork and cooperation with each side and each person willing to give and not just get can our many serious problems be solved. Prices are but one of these problems but even here neither industry nor labor alone can correct this condition.

America was made by men willing to sacrifice for the common good. Our way of life we owe to those immortals. Have we so soon forgotten their lives and their example that we ignore the fact that each generation owes its progress to those who went before? What are we now arranging for posterity? Not one of us can ignore the question and everyone should be vitally concerned.

L. F. Tice

BY-PRODUCTS OF ATOMIC ENERGY FOR USE BY THE PHARMACEUTICAL PROFESSION *

By Paul C. Aebersold, Ph. D.**

Introduction

WORLD-WIDE attention has been imperatively and justifiably drawn to the military and political problems created by atomic energy developments. Sight must not be lost also of the truly great potentialities that these same developments hold for peaceful applications to human welfare. Indeed, it is because of the promise of vast peaceful benefits, as well as the impracticability of suppressing on a world-wide scale all atomic energy research, development, and application, that a world control system must be brought about for atomic energy which permits the broadest scope of peaceful pursuits without engendering atomic warfare.

Three main avenues are now apparent in peaceful directions: (1) pursuit of fundamental atomic research, leading most likely to further constructive applications and certainly to advances in human knowledge; (2) development of useful power, leading to possible economic and sociological gains; and (3) use of radioactive products, leading to knowledge and beneficial applications in a wide range of scientific, industrial, and medical fields.

Keen interest is doubtless shown by the members of this association in all phases of atomic energy developments. It is natural however that you should be especially interested in those aspects of greatest concern to the manufacture and use of pharmaceuticals. In the broader aims of the group this means interest in all applications concerned with the general public health. We shall proceed immediately therefore to bring out these applications.

As you have heard from the previous speakers, atomic energy can be controlled in a chain-reacting pile and in this reactor there are produced intense penetrating radiations and copious quantities of a wide variety of radioactive materials. Some varieties of radiations and

* Read before the American Pharmaceutical Manufacturers' Association, December 10, 1946.

** Chief, Isotopes Branch, Research Division, Atomic Energy Commission, Oak Ridge, Tennessee.

radiomaterials result from the fission process and inescapably accompany the chain reaction. Others can be created in a secondary manner by using the primary pile radiation. These radiations and radiomaterials, whether accompanying or resulting from atomic energy processes, are of importance to the makers as well as the users of pharmaceuticals.

Radiations

Intense beams of penetrating radiations, gamma rays, fast neutrons, and slow neutrons can be obtained directly from the pile. Alpha rays, beta rays, gamma rays, and x-rays can be obtained from pile-produced radioactive materials. All of these radiations can be obtained in a wide range of energies and intensities. They can be applied to materials, organisms, and animals, as well as human beings. Effects ranging from alteration to injury and destruction are observable. In human beings the application may be in search of therapy, a circumstance in which the injury to unwanted tissue is notably greater than to essential normal tissue. Pile radiations can be applied only externally to the material to be irradiated. Radiomaterials may however be used either externally as a source of radiation or may be administered internally.

The pharmaceutical profession can become involved in the applications of radiations by:

(1) Preparation and testing of specific localizing compounds. The aim is to find a compound, which, by preferentially localizing in diseased tissues, will result in much greater radiation damage to diseased than to normal tissues. The compound could produce this result either (a) primarily or (b) secondarily. (a) The primary manner is to incorporate a suitable radioactive element into the localizing compound. The active compound would then irradiate specifically the diseased tissues. This possibility will be considered more fully in the section on radioactive materials. (b) The other possibility is to incorporate into the localizing compound an element which under exposure to pile radiation becomes a secondary source of much energy. The latter could be accomplished by the specific localization of compounds containing boron, lithium, or uranium. The isotopes boron 10, lithium, and uranium 235 readily release large amounts of energy (by nuclear disintegration or fission processes) when irradi-

ated with slow neutrons. By using materials enriched in the particularly effective isotope one can minimize the amount of compound that would have to become localized. (It is interesting to note here that by using radioactive forms of an element the localization of a compound containing the element can be traced.)

(2) Production of modified forms of materials, viruses, organisms, etc. New strains of bacteria or viruses may be produced by irradiation. Also bacteria and other organisms may be put into an inactive state or destroyed.

(3) Studying the nature and method of treatment of radiation damage. Drugs and supportive treatment should be developed to alleviate radiation sickness and to promote recovery from radiation damage. This is important not only for radiation therapy but for possible human overexposure in atomic energy work or warfare. If the radiation damage is resulting from internally absorbed radioactive material, a means may be sought of promoting elimination from the body or harmless combination in the body of the radioelement. If the damage is caused by external radiation, a counteracting agent may be sought to reduce the effects of tissue breakdown products.

(4) Analysis of materials, molecular structure, etc., using, for example, the special absorption and diffraction properties of slow neutrons.

Radioactive Elements

Radioactive atoms, called fission products, result from the process of nuclear fission itself. The splitting of heavy nuclei like those of uranium 235 results in randomly distributed fragments of lighter nuclei. These are highly unstable nuclear forms ranging from about zinc (element 30) to europium (element 63). Subsequent transformations of the highly unstable forms give rise to a total of over 150 radioactive forms of ordinarily non-radioactive elements, encompassing elements 30 to 63. There is great variety to be found in the periods of decay and other radiation properties among all these forms.

Neutrons, fundamental neutral particles of the nucleus, are given off during the fission process. Since they are uncharged particles, they can readily penetrate into the nuclei of all elements. By bombardment of elements with neutrons resulting from fission, that is

with the radiation of the chain-reacting pile, radioactive forms can be produced of all the stable elements (as well as new forms of the naturally radioactive ones). The total number of forms of radioactive atoms producible in a chain-reacting pile, including those from both fission and neutron bombardment, is well over two hundred. Many of these forms have properties that make them unsuitable for applications, but as will soon be discussed there is available a wide choice of useful forms.

Various atomic forms of a given element can arise because the nuclei of the atoms can exist with different weights. Species of atoms of the same element (same atomic number) which have nuclei of different weights are called isotopes. Instead of referring to "various nuclear forms" of atoms of an element, as above, we will refer to them technically as "isotopes". If the nuclear weights differ from those of the naturally existing stable isotopes, the isotopes are unstable or radioactive.

Because radioactive isotopes have the same atomic number, hence the same atomic arrangement of electrons, as the stable isotopes of an element, they are chemically indistinguishable from the latter. Only by means of special physical phenomena which depend on mass differences of nuclei and by the use of sensitive equipment can differences of behavior of isotopes be demonstrated. In chemical and biological processes differences are not observed in the behavior of isotopes of the same element. An exception is found to a certain extent in the case of the isotopes of the lightest element, hydrogen. Here, because of the relatively great difference in mass of the isotopes (hydrogen, mass 1, and deuterium, mass 2, occur naturally and tritium, mass 3, is artificially produced), differences are noted in reactions in which the rate of transfer of the hydrogen atoms is involved. In spite of the relatively great mass difference, however, the relative content of the two natural isotopes of hydrogen has been found to be the same in water, compounds, plants, and animals all over the world.

In Table 1 are listed some pile-produced radioisotopes which are of particular value in biological, hence pharmaceutical, investigations. It is to be noted that there are useful radioisotopes of nearly all the major elements which occur in the body (notable exceptions being oxygen and nitrogen, for which heavy stable isotope tracing methods can be employed). There are radioisotopes of many more elements than shown, some of which may enter into special uses in pharmaceutical compounds.

It can be seen that the half-life (period for one-half of the material to decay) and the radiations emitted vary considerably. In some cases the properties may not fit intended uses as well as may be desired, but in many instances the properties have special advantages. One particular value of radioisotopes of short half-life, for example, is that they will soon disappear from the system studied, thereby not giving rise to long term radiation damage in that system (human, for example) or not presenting the problem of long-lasting radiocontamination to the experimenter.

The radiations emitted by radioactive isotopes permit (1) use of the isotopes for delivering radiation and (2) quantitative detection of the isotopes with sensitive radiation measuring equipment. The first circumstance makes possible the use of radioisotopes for radiation therapy, while the second allows them to be traced and measured in all reactions in which they may take part.

Radioisotope Therapy

Radiation is in a sense a drug. It causes biologically-active products to be released in the organism as a result of the passage of ionizing particles through tissue. The nature and the mode of action of the chemical products or active agents originating from such tissue ionization are, however, not understood. Drugs, such as the nitrogen mustards, can no doubt be found which will produce effects similar to those of radiation. On the other hand, radiation may produce its effective agents in a unique disposition throughout the tissues. Moreover, a considerable variety of agents may be formed. Radiation consequently can produce unique biological results, not readily duplicable by administering drugs.

The use of radioactive isotopes for delivering radiation to diseased or malignant tissues of the body carries even further the idea of administering radiation as a unique and potent drug. The ultimate aim here would be to administer the radiation, and its consequent biological action, almost solely to the diseased tissues. This could be achieved by attaching a suitable radioactive isotope to a material which would localize specifically in those tissues. It is to be emphasized that the localizing material need have no drug effect in itself; it need merely serve as a carrier for radioactivity, only a small amount of which is necessary to produce considerable effect.

Physical localization of radioactivity would be possible in accessible tissues by a number of means; for example, by locally applied

"needles", foils, ointments, and insoluble compounds. It is difficult, however, by physical localization to provide uniform dosage over the diseased tissue; also such localization is not usually feasible for inaccessible or generalized conditions. Physiological or biochemical localization is therefore the therapeutic goal.

One can of course point out that the same goal may be sought by looking for a chemotherapeutic or antibiotic agent which, without using radiation, will localize and produce the desired therapeutic effect. Success in this direction is of course most likely. There are however three points to consider: (1) Chemotherapeutic or antibiotic agents have been most effective against organisms foreign to the body; such organisms no doubt have chemical and metabolic reactions quite different from cells of body tissues, diseased or normal; (2) a compound normally harmless but necessary to the cell, such as some amino acid or nucleo-protein, may be selectively used by the diseased or unwanted cells; only by making the compound radioactive would it injure the unwanted cells; (3) the number of radioactive atoms (or labeled molecules) that need to be delivered to a cell to produce a radiation effect may be much less than the number of molecules of a chemical or biological agent; for example, one ten-millionth of a gram of radioactive iodine atoms absorbed in the thyroid will produce a marked physiological effect from radiation.

The other speakers here have discussed most completely and authoritatively the therapeutic and clinical investigations in which radioisotopes are being used. It would be inappropriate therefore to discuss further the clinical aspects. For the sake of completeness of this paper, however, let us set down some examples in which radioisotopes localize in or metabolize more rapidly in certain tissues, namely:

(1) Bone marrow and blood forming organs. A number of radioelements localize in or metabolize more rapidly in these tissues, e. g., some of the fission products and radiophosphorus. Although the degree of localization or selective irradiation is not great with radiophosphorus used as phosphate ion, its use does result in worthwhile specificity in some cases and the material can be administered with considerable safety. The relatively short half-life of P 32 and its rate of turnover in the body reduce considerably the possibility, always present with radioisotopes, of overdosage. P 32 has become the

method of choice in many clinics for treating polycythemia vera. It is also useful in the control of some types of chronic leukemia.

(2) Lymphatic tissue and phagocytic cells. To achieve maximum localization in this case attention is being given to using colloidal particles into which a suitable radioisotope has been incorporated. The principle involved is the use of a particle size which will be selectively absorbed and retained by the unwanted cells. Colloids of chromic phosphate (labeled with P 32) and metallic gold (labeled with Au 198) are being studied. Good results are being reported with the radiogold colloid. The short half-life of Au 198, 2.7 days, has certain advantages in therapy but makes difficult the supply problem.

(3) Thyroid tissue. If the tissue is manufacturing thyroxin, the selective absorption of radioidine can be very great. The localization can result in factors of 100 and more times as much radiation dosage of the iodine-metabolizing tissue as of other tissues. To determine whether the tissues are effectively absorbing iodine a tracer dose of radioiodine may first be employed. I 131 has proved valuable in the diagnosis and treatment of certain thyroid disorders, particularly hyperthyroidism. In perhaps 20 per cent of the cases of thyroid cancer some control of the malignancy may be gained through the use of radioiodine.

(4) Blood. Radioiron will of course localize to a considerable extent in hemoglobin, hence in red cells. Therapeutic application of such localization has not been reported.

(5) Bone. Bone cells, particularly the fast metabolizing cells, will take up considerable quantities of radioactive calcium (or strontium, which behaves like calcium). Experimental trials of the take-up of the radio-material have been made in only a few cases of bone tumor. The differential absorption by cancerous as compared with normal bone cells has been noticeable but not great. Further tests are desirable.

The tests of therapeutic measures as indicated in the examples above have in all cases involved the administration of the isotope as a simple inorganic compound. It is not surprising that administered in this manner the selective pick-up by cancer cells is not great. Much more hope for selective action is placed in tests now under way in sev-

eral laboratories of the pick-up of a vast variety of organic compounds into which suitable radioactive isotopes are incorporated.

It should be noted that although specific localization offers the most unique opportunities, generalized whole body irradiation can be easily and effectively administered with a radioelement, such as radiosodium, which diffuses generally throughout the body.

Radioisotopes as Tracers

No group should be quicker to awaken to the unique opportunities afforded by radioisotope "tracer" techniques than the pharmaceutical profession. Many of the most complex problems of drug manufacture and drug action can be ideally attacked with tracer techniques; in fact, many will be soluble practically by no other means. Before bringing overwhelming evidence to bear on these points, let us consider for a moment the tracer techniques.

The profession has long been familiar with tracer experiments of a kind, for example, with the use of dyes to study blood volume and circulation, kidney function, etc. Here one marks or labels the material to be traced with a color or an indicator which can be detected with considerable sensitivity. Tracing drugs in metabolic and excretion processes has been accomplished by the use of sensitive methods of detection of the drug, or its components, in tissues and excretions. Such tracer techniques, however, often leave much to be desired for the following three reasons: (1) They are not always specific; that is, one is not certain he is tracing the substance he wishes to study; (2) The detection of the item traced is not sufficiently sensitive for many purposes; and (3) Intermediate steps or details of the process cannot be followed. The labeling or marking of the item to be traced by means of a radioisotope removes these difficulties. Radioisotopes permit the tracing of elements, molecules, particles, or bulk material with the ultimate in specificity, sensitivity of detection, and attention to complexity of detail.

Since a radioisotope of an element behaves identically with the other isotopes of the element in all chemical and physiological processes, it labels unequivocally the particular atoms one wishes to trace regardless of their incorporation into units (molecules, ions, etc.) with other atoms. The specificity of the label is even greater than detection of a species of atom—one can trace a particular batch of a certain kind of atoms. For example, one can label the calcium atoms

in a particular glass of milk and then be able later to distinguish these calcium atoms from those already in the body or those taken into the body in subsequent food.

The sensitivity of detection of radioisotopes is phenomenal, surpassing in sensitivity even the remarkably sensitive reactions of many organisms, allergic responses and even spectroscopic analysis. Less than 100,000 atoms or roughly a billionth billionth (10^{-18}) of a gram can often be readily detected in tracer experiments. Some isotopes are more difficult to detect, requiring the presence of several million atoms (say 10^{-11} gram), but in any case the number of atoms required is far from that detectable by weighing or by chemical analysis.

The complexity of processes traceable with radioisotopes is almost unlimited. The labeled atoms can be traced through a labyrinth of reactions and systems: from fertilizer to plant, plant to animal, animal to man, etc., from carbon dioxide to glucose, from glucose to fat, etc. In organic processes, the carbon atoms in a particular location in complicated molecules may be labeled and it is thereby possible to study the change of carbon atoms from this location to other molecular locations or components.

It should now be apparent why the radioisotopic tracer technique is such a particularly applicable tool in pharmaceutical studies. Namely, by the very nature of pharmaceuticals their study often calls for the greatest specificity and sensitivity of detection and the unraveling of extremely complex processes. To trace in the body agents, such as vitamins, hormones, antitoxins, etc., which appear normally in tissues in such minute quantities, is difficult or impossible by ordinary analytical methods. By labeling the agent during its synthesis with an appropriate radioisotope, for example, Carbon 14, it would be possible to detect minute quantities and to determine unknown phases of its biochemical action.

Although radioisotopes are especially appropriate for tracing the history of a pharmaceutical or biological agent itself (for example, its synthesis, absorption, excretion, alteration, breakdown, etc.,), they can also be extremely useful in studying the physiological changes induced by it. Studies can be made by means of radioisotopes of the metabolism, with and without the influence of the agent, of a wide variety of elements and compounds in various organs and tissues. One may observe the effect of a certain drug on the rate of turnover and excretion of certain essential minerals or organic compounds.

Radioactive iodine can be used, for example, to study the effect of a thyroid blocking agent, such as thiouracil. The drug would not be labeled but would be used to produce the desired physiological change, then the labeled item whose metabolism is to be studied would be introduced and traced.

In the search for an effective therapeutic radioactive compound which will localize in diseased cells and tissues, as discussed previously, the tracer technique is again unique. By using small quantities of the radioactive compound to be tested its properties of localization can be determined; likely candidates can then be administered in sufficiently large quantities to observe their radiation therapeutic value. It is common practice, for example, in certain thyroid conditions to administer first a tracer quantity of radioactive iodine, then on the basis of the measured retention of radioiodine to administer a quantity sufficient to produce the desired action. In this connection the radioisotope can serve as a double edged tool.

Of even greater importance, but perhaps not as direct an application to pharmacology as tracing pharmaceutical action or studying physiological changes induced by pharmaceuticals, is the enormous wealth of fundamental knowledge that will be gained in the physiology and biochemistry of the body both in normal and abnormal conditions. By learning what is going on biochemically in organs and tissues under all kinds of conditions, new pharmaceutical approaches to medical problems will inevitably be developed.

Availability

It is not intended here to give the impression that radioisotopic applications are new. Most of the pile-produced radioisotopes now being distributed were known and used in investigations before the war. In 1934, 12 years ago, it was discovered that radioactive isotopes could be induced in ordinarily stable elements. Phosphorus 32, for example, has been used in clinical investigations for about 10 years and is now employed rather routinely in many clinics. More than a score of research groups were before the war using radioisotopes regularly in biological and clinical investigations. Hundreds of valuable publications have appeared in which radioisotopes were used as the key research tool. What then have the new developments of atomic energy brought into this field? Although many new isotopes and techniques have been introduced by recent developments,

the outstanding answer is markedly increased availability of the useful radioisotopes.

Before the advent of the pile most radioisotopes were produced by cyclotron bombardment. As noted, a great deal of research was done and extremely important results were achieved with the isotopes thus produced. Many hours of cyclotron bombardment were, however, required to produce some of the most useful isotopes and the quantities produced were not only expensive but often did not permit the scope of experimentation desired. Here is where the pile has opened the door to a vastly greater use of radioisotopes Those isotopes which can be produced by slow neutron irradiation can be obtained from the pile in quantities thousands to billions of times greater than from the cyclotron.

Take, for example, Carbon 14. Since carbon enters into all life processes and is fundamental to the great and productive field of organic chemistry, Carbon 14 can be expected to lead to immeasurable increases in fundamental knowledge and human welfare. Yet to produce a millicurie of Carbon 14 by normal cyclotron methods would require at least five efficient cyclotrons running continuously for a year (2000 total days' bombardment) at a final cost of around a million dollars. With the pile, on the other hand, hundreds of millicuries of Carbon 14 will readily become available. In the first four months of national distribution, the Manhattan Project had already distributed about 50 millicuries of Carbon 14, which according to the above normal cyclotron production figures would require 250 cyclotron years. By special bombardment procedures the cyclotron efficiency of C 14 production could probably be increased by a factor of 10 or even 100. Nevertheless the cyclotron production would be laborious, limited and costly (probably not below several thousand dollars per millicurie). The initial production cost of Carbon 14 using the pile has been around $400 per millicurie, but increased production will lower this cost significantly. Without the pile the use of Carbon 14 would probably have been limited to microcurie quantities and to only a small number of investigations.

In some cases the increase in availability of radioisotopes by pile production is much greater even than for Carbon 14. On the other hand many isotopes are not producible with the pile at all. The pile can produce on a great scale only those isotopes resulting from fission and from slow neutron irradiation. Very fortunately indeed most of

the radioisotopes of importance in biological investigations, such as H 3, C 14, Na 24, P 32, S 35, Cl 36, K 42, Ca 45, Fe 55, Fe 59, Cu 64, Zn 65, Br 82, Sr 89, and I 131, are producible in quantity with the pile. The cyclotron is, however, a much more versatile instrument in producing isotopes because of the great variety and energy of the nuclear projectiles which it can employ.

One should not underrate the great scientific value of the cyclotron because it cannot produce certain isotopes as copiously and economically as a pile. The cyclotron is not competitive with but complementary to the pile, and is absolutely essential to many types of investigations. Certain useful isotopes, such as Be 7, Na 22, V 49, Mn 54, and As 74, are not significantly producible with a pile, but are readily prepared with a cyclotron. The pile, like the cyclotron, is of great value in atomic energy researches, but for the scale of radioisotope production demanded by scientific research the pile is absolutely essential.

Radioisotopes are now being distributed by our facilities for use in nearly all fields of research—agriculture, animal husbandry, bacteriology, botany, biochemistry, chemistry, dentistry, entomology, horticulture, medicine, metallurgy, petroleum engineering, pharmacology, physics, physiology, radiology, soil science, surgery, toxicology, veterinary medicine, and zoology. Several hundred shipments of pile-produced radioisotopes have already been made in the first few months of distribution to universities, medical institutions, government laboratories, and industrial research groups all over the country. In addition to the completed shipments requests are being received from scores of other groups not only in the United States but all over the world. Perhaps 50 per cent to 75 per cent of the work being done with these radioisotope shipments is of direct or indirect interest to the medical, pharmaceutical, and public health fields. Production of radioisotopes is being increased such that all requests for legitimate uses can be readily filled.

Commercial Aspects

As manufacturers you will naturally be interested in the commercial aspects of the field of radioisotope applications. Let me hasten to point out in this connection that there is no immediate prospect of large scale production of a therapeutic agent. We have here now no "miracle drugs", such as penicillin, streptomycin, and sulfa com-

pounds, which will require manufacture by the ton. The potency of radioisotopes as therapeutic agents or as tracer tools stems from the extremely minute quantities which are required. One gram of Iodine 131 atoms, for example, would represent an activity of about 100,000 curies or enough to treat 10 million or more cases of hyperthyroidism. Even in the case of a long half-life isotope, such as Carbon 14, one gram of the active atoms represents curies of activity and is enough material to support a very extensive amount of investigation.

To procure a gram of radioactive atoms it may of course be necessary to irradiate and chemically process a considerable number of pounds of target material. At present, however, the use of radioisotopes is in the millicure and multi-millicurie range, so that the required processing facilities are still on a very modest scale. Even with demands at 100 to 1000 times those at present no huge processing plants would be required.

Although the business of producing and extracting radioisotopes may not in itself become a large scale enterprise in the near future, there is a possibility that the production of radioisotope labeled compounds may develop into commercial magnitude. At present labeled compounds are made only on a laboratory scale for research purposes, each research group performing its own syntheses. This results in duplication of syntheses by numerous groups, thus wasting research effort; moreover, there is less overall economy in the use of valuable isotopes. As the demands for labeled compounds increase there will be an opportunity for agencies to furnish such compounds on a production volume similar to that of supplying rare chemicals and special organic compounds.

Should there be discovered the hoped-for agent, which will localize in and therapeutically irradiate malignant tissues, then it is possible that a compound containing radioactivity might require production on a sizable scale.

It must be emphasized in any case that even without the incorporation of radioisotopes into marketable products, these isotopes will contribute tremendously to the progress of the pharmaceutical field with inevitable gain to the pharmaceutical industry as well as to the customer. The manufacturer will, for example, improve his production processes and the quality of his product by using tracer techniques for developing better methods of processing and of product control. Research groups will employ tracer techniques to learn more

about pharmaceutical action, thereby leading to new and more efficient agents and methods of application. Radioisotopes will continue to be important to the industry as long as anything is not understood in the processing or use of pharmaceuticals.

Radioisotope Research Requirements

In essence the use of radioisotopes is quite simple. In practice the achievement of sensitive and exact measurement requires, as with other potent research tools, learning the "tricks of the trade".

TABLE 1*

BIOLOGICALLY-USEFUL RADIOISOTOPES PRODUCED WITH CHAIN-REACTING PILE

Isotope	Half-Life	Beta Ray Energy Mev.	Gamma Ray Energy Mev.
C 14	5000 y	0.145	...
Na 24	14.8 h	1.4	1.4, 2.8
P 32	14.3 d	1.69	...
S 35	87.1 d	0.17	...
Cl 36	10^6 y	0.66	...
K 42	12.4 h	3.5	...
Ca 45	180 d	0.3	...
Fe 55	4 y	K	...
Fe 59	44 d	0.26, 0.46	1.1, 1.3
Co 60	5.3 y	0.3	1.1, 1.3
Zn 65	250 d	0.4 β^+, K.e$^-$	1.14
Zn 69	13.8 h	I.T., 1.0	0.439
As 76	26.8 h	1.1, 1.7, 2.7	0.57, 1.25
Sr 89	53 d	1.5	...
Sr 90	25 y	0.6	...
I 131	8.0 d	0.6	0.367, 0.080
Au 198	2.7 d	0.8	0.12, 0.44
Hg 197	64 h, 25 h	K.e$^-$, K.e$^-$	0.075, 0.13, 0.16
Hg 203, 205	51.5 d	0.3	0.28

* Complete tables of the isotopes available from Commission facilities are given in *Science 103*, 697-705 (1946), and in *Reviews of Scientific Instruments 17*, 348-349 (1946). More up-to-date information may be obtained from the Isotopes Branch, Atomic Energy Commission, P. O. Box E, Oak Ridge, Tenn.

An absolutely essential factor is the employment of safe health protection measures in regard to radiation and radioactivity. In fact, assurance of safe health practices in the handling and use of radiomaterial is a prerequisite to the allocation of such material from our facilities. No technique or requirement is, however, very difficult to acquire. Hundreds of persons were trained for safe and quantitative work with radioactive materials on the Manhattan Project.

An experienced group cannot expect to rush directly into large scale work with radioisotopes. It also may not be possible immediately to obtain an experienced person to work with the group. This means that a qualified candidate must be chosen from within the group or elsewhere and sent to an experienced laboratory for training in the required techniques. Atomic Energy Commission laboratories are currently engaged to capacity on research, development, and production problems; consequently, consultation and training service cannot immediately be offered on radioisotope techniques within Commission facilities. There are, however, scores of groups in universities and elsewhere experienced in radioisotope investigations. Arrangements are often made for the participation of persons in such groups with a view to acquiring radioisotope techniques. A number of institutions are already offering courses in this field and more will surely follow suit in the near future.

The newly inaugurated Atomic Energy Commission will no doubt give much consideration to the part it can take in the training of personnel in radioactivity techniques as well as in all phases of atomic energy. Allocation of radiomaterial for training purposes has since the initiation of distribution been afforded high priority. After a short period of training with an experienced group a person can work with small amounts of activity in his own laboratory and acquire further experience while doing his own research. Training opportunities will certainly be available in proportion to the interest shown in obtaining such training.

The situation in regard to the commercial procurement of adequate instrumentation, both for radioactivity measurement and health protection, is improving rapidly. Suitable instruments are now available on purchase at reasonable prices. Increased demand is accelerating the availability and development of good instruments.

Thus, although many research groups may not be able to undertake immediately a program with radioisotopes because of lack of ex-

perienced personnel and instrumentation, there is little need for a progressive group to long delay in taking steps to use one of the most important research aids ever developed.

Conclusion

Tracer isotopes will eventually shed light into all the dark labyrinths traversed by atoms in going about their business in the healthy or unhealthy body. The pharmaceutical profession, in cooperation with the other professions, will be peering and delving into the tracer-lighted mazes to bring forth new applications for public health and welfare.

BOOK REVIEW.

Chemotherapeutic and Other Studies of Typhus. By M. van den Ende, C. H. Stuart-Harris, F. Fulton, J. S. F. Niven with others. Special Report Series No. 255. Medical Research Council. 246 pages + ix plates. His Majesty's Stationery Office, London. Price, 12s. 6d. ($3.65, British Information Services, 30 Rockefeller Plaza, New York 20, N. Y.)

This book represents the published clinical and laboratory studies on typhus fever undertaken by the National Institute for Medical Research (London).

The work is divided into five parts. The first chapter is concerned with the toxicity of two compounds V-147 (*para*-sulfonamidobenzamidine hydrochloride) and V-186 (*para* sulfonamidobenzamidoxime hydrochloride) found to be most effective in the treatment of experimental typhus in mice. The second chapter reports on the chemotherapeutic trials of these drugs in man. The last three parts of the book are devoted to various immunologic aspects of typhus.

Those working on the rickettsial diseases will find this publication of great value in reporting the extensive findings by these various research teams in the study of typhus fever.

L. F. Tice.

WAKSMAN AND STREPTOMYCIN

By T. Swann Harding

SELMAN A. WAKSMAN of the New Jersey Agricultural Experiment Station at New Brunswick is a little Russian-Jewish soil microbiologist who has been in this country quite a while. He has a fair growth of whitening hair, an iron-gray mustache, is short, a bit inclined to the moderate stout shape, affable, approachable, and completely without pretension. He heads his own department of soil microbiology at an annual salary which would bring a loud laugh from the average research man in private enterprise.

He works in the typical economically fashioned and equipped laboratory structure occupied by any number of patient research workers in our land-grant colleges the country over. For, in 1887, a law was passed which provided Federal funds for research to be performed in the State agricultural experiment stations. Subsequent enactments somewhat increased these funds, but they are still far from munificent, though the Agricultural Research and Marketing Act of August 14, 1946, will multiply them four times.

For something like thirty years Waksman did excellent but unspectacular work on a wide variety of soil organisms. Then within the last few years he hit on streptomycin, fame focused its spotlight on him, invitations to speak all over the country poured in, and the American way of life for the famous threatened to end his way of life as a quiet research worker. Today private enterprise is spending $20,000,000 for edifices appropriate to the manufacture and testing of streptomycin, and invitations for addresses pour in upon the unhappy discoverer at a rate of one a day.

Dr. Waksman has no ambitions to become a high-priced high-pressure expert for some commercial drug company. He would like to see the profits from his discovery plowed right back into research. He coined the word "antibiotics" and when some reporter, seeing it in the President's budget message, concluded it was a $440,000 word, that amused Waksman, but he would like to get hold of even a fourth of that—for more research. Moreover it is mighty difficult to plan research when Los Angeles would like you to fly out there to give a 6-minute talk and the Chamber of Commerce asks for 5 minutes of

your time, then at the last minute says you are to speak 30 minutes and it will be broadcast.

Many a research worker has had his way of life similarly distorted by the making of some outstanding finding. Yet Waksman's ready streak of humor, and his entire lack of vanity, protect him from becoming either arrogant or inaccessible. Moreover he can deliver a paper really well, like the one we heard him give this morning before a symposium on Research in Antibiotics, sponsored by the Antibiotics Study Section, Research Grants Division, National Institute of Health, U. S. Public Health Service—if you must know!

Waksman's title was: Antibiotics of Actinomycetes, with Special Reference to Certain Challenging Problems, Notably the Development of Bacterial Resistance. He was introduced as the father of antibiotics and he crammed what he had to say into a little over a half hour. He is an animated speaker. That is unusual in scientific investigators as most of them read their papers with all the animation of a mortician checking over the list of accessories for which he intends to charge the customer's unfortunate family.

The soil bacteria have long been relatively neglected micro-organisms, their study having been confined to a few specialists at agricultural institutions. But Waksman reasoned that many of them might produce antibiotics of great usefulness, and at least 20 per cent of them proved capable of manufacturing substances that would kill bacteria. However, both the soil organisms and the antibiotics vary considerably, and by no means all of the former will produce some of the latter in any medium that has been tested.

Some of the soil organisms produce substances quite different from antibiotics, too. Some of the antibiotics produced are very active against all sorts of bacteria, some are highly selective, many produce toxic substances also. Some of them will even kill fungi. But the production is inherent in the medium, not in the strain. Sometimes a micro-organism must be tested in as many as 120 different cultures before it will find one in which it can produce an antibiotic.

Moreover, the antibiotics produced are characteristic of the cultures, not of the strain of micro-organisms—not even of the genus or species, for that matter. It is the cultural environment in which the soil micro-organism grows that determines its ability to produce substances which will kill bacteria, and some have produced nothing at

all though they have been grown for more than 30 years in all sorts of cultures. Some will produce richly on one culture, not at all on another, and streptomycin can be produced also by wholly different species. Finally, many different antibiotics can be produced and that may prove of great value in future work.

Four important problems today face research workers in this field and the most important certainly is the development of bacterial resistance to antibiotics like penicillin and streptomycin. Moreover, since the latter is used largely in the treatment of chronic infections, like brucellosis and tuberculosis, thus giving the causative organisms ample opportunity to develop and fortify resistance, the condition is very serious here.

Again, no one as yet knows the precise mode of action of antibiotics. Precisely how do they slay bacteria? Is it a chemical or a physical action, seated deep in the molecules? Why does strain resistance develop? Are antibiotics selective in action? How is it that antibiotics which are so lethal to bacteria are often harmless to the body cells? Little indeed is really known about how they act on bacteria.

Thirdly, the isolation of new antibiotics must be pursued with great intensity. Some are inclined to say that we have these two, penicillin and streptomycin, and the chase is ended. Instead Waksman believes that the search has just begun for substances capable of killing all, even the most resistant bacteria, and of seeking out only certain micro-organisms selectively and destroying them.

Fourth, there must be persistent and intensive search for antibiotics capable of killing viruses.

In any group of a hundred million germs possibly 500 will resist a certain antibiotic, regardless of the strength in which it is used. The job is to find antibiotic strains, or new antibiotics, which will certainly kill even the most resistant of the organisms. Resistance of micro-organisms in the bodies of human beings under treatment offers a critical problem indeed. Moreover different bacteria develop resistance at different speeds. Then how do they do this? There are at least three reasonable hypotheses.

First, possibly the antibiotic selectively kills cells of low resistance, leaving those few of higher resistance better opportunity than ever to proliferate.

Secondly, possibly the micro-organism develops an alternative physiological mechanism of living and growing under certain adverse conditions. Possibly it replaces one physiological method of survival with another. When the primary mechanism breaks down, a secondary physiological mechanism supplants it, perhaps involving also some variations in enzyme action.

Lastly, it may just be a matter of genetic mutation with the periodical development of sports of vastly enhanced resistance. In any case populations of specific resistance levels can be produced and built up.

Thus Waksman outlined the problems confronting research workers in antibiotics and possible means of solving them. There is urgent need for different, stronger, and more selective antibiotics. Possibly the tomatin, an antibiotic agent produced from the tomato plant, or subtilin, produced by an organism which goes into high on a medium containing juice expressed from discarded asparagus butts, cut off before shipment or canning, may be the answer. They also represent work by agricultural scientists, this time by those in the Department of Agriculture itself.

E. MERCK OF DARMSTADT, GERMANY

By L. Wilson Greene *

History

THE firm of E. Merck originated as a small apothecary shop which was started in 1668 by J. F. Merck. In 1827, the owner of the business at that time, H. E. Merck, began the manufacture of chemical preparations on a commercial basis. These first products were mostly alkaloids extracted from crude drugs.

The number of alkaloids produced gradually increased during the next twenty-five years and in 1850 the firm began to make inorganic chemicals, followed shortly thereafter by organic compounds. Early in this century (1903), the company moved to its present location north of the city of Darmstadt, near the main highway between Frankfurt a/Main and Heidelberg.

A new research laboratory was constructed in 1922 and in 1930 a biological department was created and the manufacture of synthetic vitamins was begun. Almost a thousand patents were owned by Merck in 1937.

Products

The production activities of the firm prior to World War II were in three main categories: (1) the manufacture of pharmaceuticals and fine chemicals from basic raw materials, (2) the manufacture of pharmaceuticals and fine chemicals from intermediate products purchased from others, and (3) the purification and re-sale of products bought from others.

The first group includes ascorbic acid, dextrose and lactic acid, from starch; alkaloids extracted from natural plants from the Dutch East Indies, as well as alkaloids from opium imported from Turkey, from Spanish ephedra, and from Peruvian coca leaves; tannic acid from galls imported from the Dutch East Indies; hormones prepared

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from glandular products obtained from slaughter houses in Darmstadt and Frankfurt; vitamin D from ergosterol, made from yeast bought locally; and metallic salts, the most important being those derived from mercury and bismuth imported from Spain. Lactose metallic salts were also produced.

Intermediates purchased from plants of the I. G. Farbenindustrie A.-G. were employed to make the products comprising the second group. These were mainly barbiturates, such as Veronal, Veramon, and Phanodorn. Merck also produced salicylic acid.

The third group was quite varied and included a large number of laboratory reagents and proprietary compounds. Solvents were procured from the firm of Dr. Alexander Wacker, Gessellschaft für Elektrochemische Industrie m. b. H., in Munich.

Here are some typical production figures of Merck specialties, in pounds per month.

Betabion (vitamin B)	880
Cebion (ascorbic acid, vitamin C)	1,760
Vigantol (vitamin D)	4,400
Luminal	4,400
Veronal	2,640
Phanodorn	2,640
Salicylates	22,000
Iodides and bromides	8,800
Glycerophosphates	1,760
Lactic acid and salts	22,000
Hydrogen peroxide	4,400
Dextrose	8,800
Agricultural insecticides	22,000

Merck and C. A. F. Kahlbaum G. m. b. H. of Berlin shared what amounted to a monopoly on laboratory reagents, which are well-known throughout the world.

The firm employed approximately 5000 people in the summer of 1938. These comprised the following: 150 chemists, 150 engineers, 600 clerks, 2600 plant workmen and 1500 girls for filling and packing.

Sales Organization

Since about 30 per cent of its products were exported, the firm made sure that they conformed to the required standards of the coun-

tries to which the products were to be shipped. This meant that the laboratory had to perform many different types of inspection tests before the products were released for shipment.

Merck did not sell directly to the laboratories, pharmacists, doctors or hospitals but dealt through wholesalers only. To facilitate distribution, warehouse stocks were maintained in Berlin, Hamburg, Munich and Schönebeck. Sales offices or "propaganda depots" were located at Breslau, Düsseldorf, Hannover, Königsberg, Leipzig and Stuttgart.

The records obtained by the American occupying forces do not indicate that I. G. Farben had any ownership control over Merck, but the latter firm did have combined selling agreements with I. G. subsidiaries. For example, they had an agreement with Bayer covering the marketing of barbiturates. There was also an agreement with C. F. Boehringer & Söhne, Mannheim, for packing products in ampuls and for the production of tablets; and with Knoll A.-G. of Ludwigshafen for the sale of a large number of products under a common trade mark.

Most of the information presented here was obtained from the British document, "Germany, Basic Handbook, Economic Survey, Section J, The Chemical Industry". Further data on this organization will be found in the 55-page report, "E. Merck and Other Pharmaceutical Targets in Southwest Germany", by Erwin C. Kleiderer, Victor Conquest and James H. Williams. (Report No. PB-918, Office of Technical Services, Department of Commerce, Washington 25, D. C.)

SCIENCE AND CHARACTER BUILDING *

By Ivor Griffith, Ph. M., D. Sc.

SCIENCE is an ever solvent search for truth and it operates with the unremitting faith that the truth is worth discovering whether it hurts or whether it heals.

Said Pilate, that unwitting instrument of the greatest plan ever conceived for the redemption of the sub-angelic sons of Adam, "What is Truth?" and Adam himself, we must remember, had an inquiring mind. He too was something of a researcher; hence the apple episode and the forthwith transfer of the primal pair to Eden suburbs, leaving to us, their children, a legacy of sin and sweat.

And from Adam through Pilate to Einstein, answers to the eternal question, "What is Truth?" have been always unconvincing.

More than likely, this very same question will be the last vain mouthing of the last lone son of Adam when he disappears through the portal of the world's last sunset into the endlessness of time. Meantime, however, we do our share who even vainly search for truth and though a million old beliefs are ruined by such a search, we still search on, and time, itself, is truth's most helpful friend.

Euripedes said, "Time will discover everything to posterity. It is a babbler and speaks even when no question is put". Also we must forever remember that what is now called *"true"* is only currently *"true"*. Science is never the whole truth but rather the continued *colation* of the eternally yielding *marc* of universe with the *menstrua* of knowledge, industry and honesty. As such, it has been and is, one of the most accelerating catalysts in man's evolution but it may well prove to be his destruction too.

Dr. Raymond B. Fosdick of the Rockefeller Foundation imposes upon the scientist this challenging position in our present society, "We look to you to distinguish between that truth which furthers the well-being of mankind and that truth which threatens it." He further quotes one of the scientists who played an important role in the development of that cataclysmic, world changing atomic bomb,

* Read as part of the Presidential Address at the Annual Convention of the Science Teachers Conference of the Middle Atlantic States.

thus, "A scientist cannot hold back progress simply because of fears of what a foolish world may do with his discoveries", suggesting that it was his viewpoint that science will plunge and crash ahead in the search of truth even if the results of the search leave the world in dust and ashes.

Dr. Fosdick confesses his inability to know the final answer. He admits that to expect the scientist to foresee the application for good or for bad of new discoveries seems to be in the realm of the impossible, for practically any discovery can be used for either social or anti-social, constructive or destructive purposes.

The great German cartel was the Dr. Jekyll and Mr. Hyde on the chemical stage. Beginning with the rye industry—and possibly innocently enough—it grew to deliver insidious weapons of war; yet, out of the same industry came a host of healing agencies which continue to remove burdens of pain from the shoulders of suffering humanity. Obviously then, the good and the evil that flow from the search for truth are more often than not indistinguishable at the point of origin.

But summarizing Dr. Fosdick's attitude before going on to that aspect of the search for truth which tends to build character, he concludes that science merely reflects the social forces which surround it. Where there is peace, science is constructive; where there is war, science is perverted to destructive industry and there is no question but that the progress of the last war, and notably atomic fission, has brought humanity to the doorstep of doom and we are faced with the urgent question, "Can education and tolerance and understanding and creative intelligence run fast enough to keep us abreast with our mounting capacity to destroy?"

An answer can be most optimistically given.

The other day, for instance, I listened to Professor Feiser relate incidents within his visit to the near East in connection with extending the domain of applied science and research in science in that part of the world. He spoke of meeting scientists of all origins and nationalities and was struck wtih the fact that beyond chauvinism or nationalism or any other *ism* an unfaltering search for truth seemed to be their main objective.

There are substantial proofs as well as reasons why the search for truth involved in science, is necessarily and fundamentally a developer of character in the individual. Brusquely, let me ask you

to search your own minds for a character cross-section of a representative group of scientists and then compare it with the character cross-section of a representative group of business men, of artisans, of musicians, of professional men. Is it not the fact that the fine attributes of fidelity of purpose, of a respect for the truth, of a devotion to human welfare, of "service above self" are not more manifest in a group of true scientists than in any other group of practitioners.

True science should be the true democracy and I am inclined to believe that if we could replace the financiers, the politicians and the war mongers of the earth by a council of *true* scientists, the government of the world would take a turn for the better and it could be on earth as it is in Heaven.

I remember an old Scotch professor of chemistry under whom I studied in my early days and whose pet charge to his laboratory assistants indicates clearly the search for truth and the basic practice of honesty which is the sound foundation upon which science rests. Said old Professor Carey, over and over again to his assistants, "Report exactly what you find, not a whit more, not a whit less". What a fine motto or admonition to have on display in every laboratory everywhere.

"Character", said a wag, "is what a man has in the dark". Herein rests a great deal of primitive wisdom and certainly the search for truth which seeks to bring everything into the light confers upon one, who traverses through the dark, the challenge, that in the quiet places, in the unwatched places, his light must shine from within just as clearly and convincingly as when it is not needed with the coming of dawn.

All of this inclines me to state an opinion which I have had as a conviction over a period of years: namely, that in America, we have avoided teaching the fundamentals of science except to a few, when certain basic phases of science should be administered to every student in high school, irrespective of the fact whether there is an intention to continue through to college or not. We have gone haywire over vocational training and the social sciences and we have neglected those phases of science which might truly be considered the humanities.

Mind you, I am not questioning the validity and the value of teaching, in their proper place, the social sciences and vocational issues, but they must be corner-stoned with a basic training in the

fundamentals of those sciences which explain man's position in the universe and as Pope put it "in the study of mankind itself".

Thomas Huxley, in his inimitable definition of education, is quoted as follows:

> "That man, I think, has had a liberal education who has been so trained in youth that his body is the ready servant of his will, and does with ease and pleasure all the work that, as a mechanism it is capable of; whose intellect is a clear, cold, logic engine, with all its parts of equal strength, and in smooth working order; ready like a steam engine to be turned to any kind of work, and spin the gossamers as well as forge the anchors of the mind; whose mind is stored with a knowledge of the great and fundamental truths of nature and of the laws of her operations; one who, no stunted ascetic, is full of life and fire, but whose passions are trained to come to heel by a vigorous will, the servant of a tender conscience; who has learned to love all beauty, whether of nature or of art, to hate all vileness, and to respect others as himself."

And then there is this thought-provoking statement:

> "Education is three dimensional, for he who is properly educated must have a balanced, well-rounded knowledge of things as they are, a happy familiarity with things as they were, and beyond all, a dream of things as they might be."

I can well believe, that a man so educated could not help but show a state of heart and mind and life kindred to that so well portrayed in Channing's lovely symphonic prayer:

> "To live content, with small means; to seek elegance rather than luxury; and refinement rather than fashion; to be worthy, not respectable; and wealthy, not rich; to study hard, think quietly, talk gently, act frankly; to listen to stars and birds, to babes and sages with open heart; to bear all cheerfully, do all bravely, await occasions, hurry never.
>
> In a word, to let the spiritual unhidden and unconscious grow up through the common.
>
> This is to be my symphony."

What did Thomas Huxley mean when he referred "to a mind stored with the knowledge of the great and fundamental truths of

nature and the laws of her operation", if he did not mean that a truly educated man, whether he be a preacher or a priest, a lawyer or a stock broker, a professor of English or a chemist or any such practitioner had to be taught the fundamentals of zoology and biology, of physics, of chemistry, of mathematics and the like?

Frankly, I view the future with a great deal of concern, yet the concern would be much less if I knew that the great proportion of the world's population had been educated in the Huxley sense to an appreciation of science as the search for truth, and an understanding of our current knowledge of nature and of the laws of her operations.

The undertaking of the National Science Teachers' Association toward a better program of science teaching in America is a laudable one. I go to their little booklet in order to bring this rather disorganized address to its end, hugging closely to my insistence that science teaching breeds character.

In this little booklet we are told that the proper teaching of science to American youngsters would bring about a really ethical development of our young people toward assuming the responsibilities that will be theirs in the years to come.

I close with a paragraph, which I believe came from my pen, and which is part of the introduction to the little pamphlet entitled, *"Toward Building America."* "Such a program expresses to every American citizen the vibrant challenge that the fine tomorrow of this great democracy can only come to pass if every current generation insists on the training of its youth in such wise that the following generation will inevitably be an improvement over the generation which preceded it."

SELECTED ABSTRACTS

Treatment of Breast Abscesses with Penicillin. M. E. Florey, J. S. MacVine and M. A. M. Bigby. *Brit. Med. J.* No. 4483, 845 (1946). Eighteen patients suffering from breast abscesses were treated with a combination of intramuscular and local penicillin, the dosage by the former route being 15,000 units every three hours over a period varying from twelve hours to three and one-half days. The drug was instilled locally in a concentration of 500 units per ml.

The average healing time in penicillin-treated cases was reduced to half that required in eighteen control patients who, with two exceptions, received at least one course of sulfathiazole or sulfamethazine (20 to 30 gm.) which was begun pre-operatively. Control patients who were lactating received a course of stilbestrol varying from 30 to 65 mg. in three to five days. It was found that the use of stilbestrol was not necessary in the penicillin-treated group, and the mothers were able to continue suckling throughout the course of treatment. Suppuration was hastened by the penicillin treatment, but ceased more rapidly.

The number of operations was reduced from 22 to 4, and the total number of days during which treatment at the hospital was required was reduced from 661 to 232.

2-Thiouracil in the Treatment of Congestive Heart Failure. E. P. Sharpey-Schafer. *Brit. Med. J.* No. 4484, 888 (1946). Twelve cases of severe congestive heart failure showing no response to therapy with bed-rest, digitalis or mercurial diuretics were treated with 2-thiouracil in a daily dosage of 1 to 2 gm. over periods varying from 18 to 275 days.

The author states that life may be prolonged both in the low-cardiac-output cases (valvular and hypertensive heart disease) and in the high-cardiac-output cases (heart failure with emphysema). Detailed studies on cases of the latter group are to be reported elsewhere. Despite the poor prognosis in such cases, some patients may improve sufficiently to leave the hospital despite permanent reduction of arterial oxygen saturation.

Unpublished histological studies are stated to have yielded evidence that the thyroid returns to normal after the administration of 2-thiouracil was stopped.

In tabular form are presented circulatory data on the twelve patients prior to use of the drug and the results observed following treatment.

Stability of Penicillin in Glycerin and in Glycols. R. J. Ferlauto and H. A. Clymer. *Science 105,* 130 (1947). Studies on the stability of penicillin salts in glycerin, propylene glycol and carbowax 1500 indicated that the variation observed is dependent upon the particular salt used, the solvent, and also the lot of the latter, whether or not produced by the same manufacturer.

The penicillin salts studied were the commercial calcium (CaP), amorphous sodium (NaP), and crystalline sodium (NaP cryst.) compounds. The stability of these compounds in the solvents mentioned was determined both before and after storage at 5°, 23°, and 37°.

The order of stability was consistently found to be NaP > NaP cryst. > CaP. Both CaP and NaP cryst. were almost totally inactivated by glycerin and propylene glycol at 5° within 2 hours. Under the same conditions NaP in glycerin and in propylene glycol retained, respectively, 14.5 and 81 per cent of its activity. After storage for 2 days at 5° NaP in glycerin possessed only 0.1 per cent of its activity, although in propylene glycol 21 per cent of the original potency was present after 7 days.

The rate of inactivation in Carbowax 1500 was much lower than that noted for the other two solvents. After storage for 13 days at 5°, the percentage activities of the penicillin salts in this solvent were as follows: CaP 2, NaP cryst. 81, and NaP 98. Much lower values were observed for samples stored at 23° and 37°.

All three penicillin salts were found to be more stable in the first two fractions (25 and 50 per cent of the total volume) of redistilled propylene glycol and less stable in the residue than in the undistilled solvent.

Results of Rapid Treatment of Early Syphilis. J. R. Heller, Jr. *J. Venereal Disease Inform. 27,* 217 (1946). The author presents a progress report on the treatment of approximately 8,000 cases

of early syphilis handled at rapid treatment centers. Eleven schedules of treatment were employed, in the majority of which penicillin in varying doses was administered either alone or in conjunction with mapharsen and/or bismuth. Included also were the following technics: multiple injections of mapharsen and bismuth for 11-20 days; the five-day intravenous drip method for mapharsen; and the eight-day intravenous drip method for mapharsen and bismuth.

In a series of cases which received posttreatment observation for 15 months, no significant difference was noted between the schedules in which penicillin was administered alone and those in which smaller doses of the antibiotic were given in conjunction with mapharsen.

Among a group of cases observed for 10 months, the most effective results were secured from the use of 1,200,000 units of penicillin with adjunctive mapharsen and bismuth.

There were no deaths attributable to the administration of penicillin alone. When it was used in combination with small amounts of mapharsen and bismuth, the mortality rate was one death in 4,312 cases. The mortality rate resulting from intensive arsenotherapy was one per 149 cases in the 5-day intravenous drip method and one per 1,873 cases treated by multiple injection.

Because of the toxicity and relatively high mortality rate resulting from massive arsenotherapy, this form of medication was largely discontinued by the rapid treatment centers which participated in this study after preliminary observations indicated that favorable results might be obtained from schedules relying principally on penicillin.

Studies on the Stability of Streptomycin in Solution. E. J. Oswald and J. K. Nielsen. *Science 105,* 184 (1947). In order to determine the most efficient concentration and pH level for a solution of streptomycin to be used as a working standard, the drug was dissolved in sterile 0.05M potassium phosphate buffer at pH levels of 6.0, 7.0, and 8.0 in quantities sufficient to produce solutions with potencies of 100 μg./ml. and 1,000 μg./ml. at each pH level.

The solutions were stored at 10° and were assayed weekly by both the turbidimetric and plate methods for a period of three months. No appreciable decrease in potency was demonstrated by either assay procedure.,

According to F.D.A. specifications for the turbidimetric assay of streptomycin the final solution to be used contains 100 μg./ml. of the drug. Accordingly, it was necessary to dilute the more concentrated solution 1:10 with distilled water to adjust its potency to the required strength, but this produced a solution in 0.005 M phosphate buffer. It was noted that an increase in the concentration of phosphate salts resulted in a decrease of the activity of streptomycin as determined by the turbidimetric method. This depressor effect appeared to be the result of two factors—buffer salt concentration and pH—and was most marked at pH 6.0. Almost normal activity reappeared at pH 8.0.

Waksman has demonstrated that buffer salts repress the activity of streptothricin in a similar manner.

Vaginal Absorption of Penicillin. J. Rock, R. H. Barker and W. B. Bacon. *Science 105,* 13 (1947). Vaginal suppositories containing 100,000 units of penicillin in a cocoa butter base were used in the treatment of 20 patients. The amount administered at each treatment was 200,000 units, and at least three determinations of the blood level of the drug were performed at intervals ranging from one-half hour to eight hours afterward.

Penicillin suppositories produced relief in nine nonpregnant patients with profuse leucorrhea and/or pruritus. It was observed that absorption seemed to be somewhat diminished during the ovulation phase, considered as including 14±2 days in the ordinary menstrual cycle. Higher drug levels were noted in patients near the end of their menstrual cycles and also in two patients who were menopausal.

Little or no absorption of penicillin could be demonstrated in three of a group of four pregnant patients who were near term. The fourth case, 2 2/3 months short of term, showed an absorption similar to that of the nonpregnant patients.

High blood concentrations of penicillin were noted in four patients who were 10 days post partum, and moderate levels in two others, respectively 14 and 35 days post partum. One patient, nine days post partum, showed a very low absorption of the drug.

Except during the last two months of pregnancy, penicillin appeared to be easily absorbed from vaginal suppositories of the type tested, ordinarily producing therapeutic blood levels for from four to six hours.

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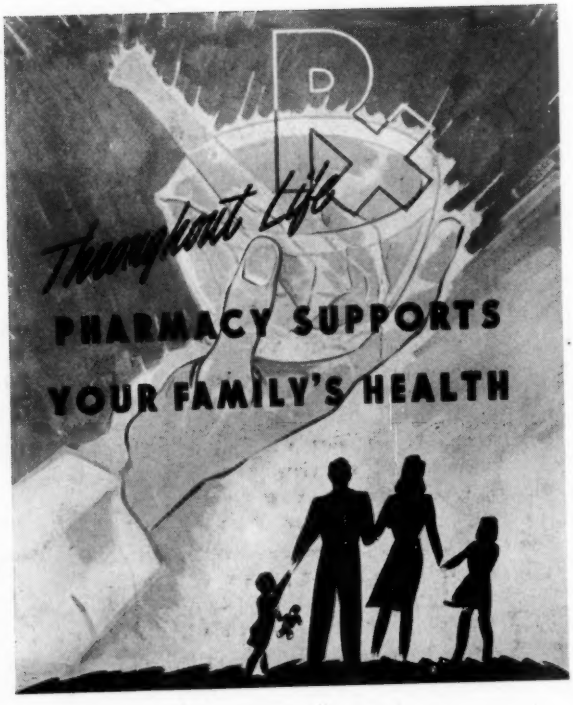
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